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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,728	07/03/2001	John F. Wironen	RTI-133	8170

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EXAMINER	
SMITH, CAROLYN L	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/897,728	WIRONEN ET AL.	
	Examiner	Art Unit	
	Carolyn L. Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-23,31 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-23,31 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and remarks, filed 7/31/06, are acknowledged. Amended claims 1 and 23 are acknowledged.

Applicant's arguments, filed 7/31/06, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1, 3-23, 31, and 37 are herein under examination.

Claim Rejections – 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-6, 13, 19-20, 22-23, 31, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Zhang et al. (Journal of Periodontology, 1997 Nov; Vol. 68(11), pages 1076-1084).

Zhang et al. disclose an *in vitro* method for quantifying the osteoinductive potential of demineralized bone matrix (DBM), which is a collection of implant material containing bone morphogenetic proteins (BMPs) and other noncollagenous proteins, from cadaverous humans

before clinical (human) use (allograft) (title; abstract; page 1077, col. 2, second and third paragraphs), as stated in instant claims 1, 3, 13, and 23. Zhang et al. disclose the DBM is processed from ground bone (page 1077, first column, last paragraph to second column, first line) which represents cortical bone, cancellous bone, or a combination thereof, as stated in instant claim 3. Zhang et al. disclose osteoinductivity of demineralized bone matrix is due to bone morphogenetic proteins (BMPs) and other noncollagenous proteins in the matrix (page 1077, col. 1, third paragraph). Zhang et al. disclose exposing ground bone (implant material) to dilute hydrochloric acid, a demineralization process to dissolve the bone material (page 1077, col. 1, last paragraph to col. 2, first paragraph) which represents the releasing step of instant claims 1, 4, and 5. Zhang et al. disclose calcium content of bone being demineralized can be demonstrated to be a linear function of pH of the solution (abstract and page 1077, col. 2, first paragraph) as well as calcium content determination (page 1077, col. 2, last paragraph to page 1078, col. 1, first paragraph) with the positive presence of calcium (abstract and Figures 1, 3, 4). Figure 3 shows calcium content less than 3%, as stated in instant claim 4. Zhang et al. disclose the bone matrices being separated into particles according to size ranges with sieves (page 1077, col. 1, last paragraph). Zhang et al. disclose combining bone cells with EDTA and trypsin (enzyme) (page 1078, col. 1, third paragraph) which represents dissolving the bone implant matrix with an enzyme, as stated in instant claims 5 and 6. Trypsin is utilized and then ALP was measured (page 1078, col. 2, first paragraph) which represents an enzyme that did not destroy osteoinductive factors present in the releasate, as stated in instant claim 6. Zhang et al. disclose quantifying the concentration of alkaline phosphatase (ALP) (implant material releasant of osteogenic factor) via a protein assay using milligram quantities (page 1078, col. 1, last

paragraph to col. 2, first paragraph) and studying changes in ALP level with time to assess effects of DBM on human periosteal cell induction using 5 mg of DBM (which contains BMPs) per flask (page 1081, col. 1, second paragraph), which represents quantifying a concentration of at least one osteogenic factor present in an implant releasate, including BMPs, as stated in instant claims 1, 19, and 23. It is noted that that the limitation in instant claims 1 and 23 that states "does not require implantation of said materials *in vivo* or use of a living biological entity" is reasonably interpreted as not requiring but not necessarily excluding *in vivo* material or a living biological entity. Zhang et al. disclose mesenchymal cell induction process (morphogenic) is frequently monitored by changes in ALP activity of cells being studied (page 1081, col. 1, second paragraph). Zhang et al. disclose noting changes in ALP concentration on curves with noted values of DBM (with BMPs) to determine osteogenic potential of implant material (Figures 6 and 7) which represents converting concentration values of an osteogenic factor to an osteogenic potential for a representative sampling whereby the osteogenic potential is realized, as stated in instant claims 1 and 23. The control curve in Figure 6 represents a predetermined curve, as stated in instant claims 1 and 23. Zhang et al. disclose proliferation effects of demineralized bone matrix were studied to assess potential mitogenic effects (page 1080, col. 2, second paragraph). Zhang et al. disclose a correlation graph between *in vitro* ALP activity (concentration) and percent calcium (probability to generate bone *in vivo*) (Figure 8), as stated in instant claim 20. Zhang et al. disclose using periosteal cells that are presumed to be responsive to BMPs actions, differentiating into osteoblast cells and correlations with ALP (Figure 8 and page 1083, col. 1, third and fourth paragraphs), as stated in instant claim 22. Zhang et al. disclose the *in vitro* assay may be a good substitute for the *in vivo* assay in assessing

osteoinductive potential of demineralized bone matrix and reducing animal use via quality assessment of produced bone products (select bone material) for clinical application (to be implanted into patient) (page 1083, col. 1, last paragraph to col. 2, first paragraph), as stated in instant claim 31. Zhang et al. disclose that *in vitro* ALP activity peaks on day 5 and the *in vitro* assay requires only 1 week to obtain information regarding osteoinductive potential of demineralized bone products (page 1083, col. 2) which represents a total time of less than about 4 days with the word "about" being interpreted broadly, as stated in instant claim 37. Zhang et al. disclose calcium contents are used as a major indicator of osteoinductivity (page 1082, col. 2, third paragraph) and Figure 8 demonstrates correlations between calcium and ALP (*in vitro*).

Thus, Zhang et al. anticipate the limitations in claims 1, 3-6, 19-20, 22-23, 31, and 37.

Applicants argue that Zhang et al. use *in vitro* assays and require living cells, whereas the instant invention "does not use a living biological entity". This statement is found unpersuasive as instant claims 1 and 23 recite "quantifying occurs *in vitro* and does not require implantation of said materials *in vivo* or use of a living biological entity" which is interpreted to mean that while the use of a living biological entity is not required, it is not prohibited from use in the invention. Applicants argue that the *in vitro* assay of Zhang et al. requires the use of cells, while Applicants' in vitro assay does not require the use of cells. It is noted that the instant claims do not prohibit the use of cells. Not requiring use and prohibiting use are very different issues and do not mean the same thing. Applicants argue that instant claims 1 and 23 now recite a Markush group of osteogenic factors which are analytes of the invention's *in vitro* assay and state that alkaline phosphatase (ALP) is not one of those analytes. It is noted that the Zhang et al. studies

of ALP were performed with DBM which contains BMPs which are osteogenic factors found in the Markush group. Applicants' arguments are deemed unpersuasive for the reasons given above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12, 14, and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Journal of Periodontology, 1997 Nov; Vol. 68(11), pages 1076-1084) as applied to claims 1, 3-6, 13, 19-20, 22-23, 31, and 37 above, and further in view of Schmidmaier et al. (Journal of Biomedical Materials Research, 2001 May; Vol. 58(4), pages 449-455).

Zhang et al. disclose the limitations of claims 1, 3-6, 13, 19-20, 22-23, 31, and 37, as stated in the 35 USC 102 rejection above. Zhang et al. do not disclose the limitations of claims 12, 14, and 16-18.

Schmidmaier et al. describe polymer degradation and erosion (mass loss of polymer matrix) and controlled release of TGF-beta 1 from a biodegradable polymer and demineralized bone matrix (page 450, col. 1, second to fifth paragraphs). Schmidmaier et al. describe osteogenic factors that are mitogenic and stimulate differentiation and maintenance of cells (page 449, col. 1, first paragraph) which represents at least one osteogenic factor comprising a mitogen and morphogen, as stated in instant claim 12. Schmidmaier et al. describe an osteogenic factor, such as transformation growth factor- beta 1 (TGF-β1) (abstract), as stated in instant claim 14. Schmidmaier et al. describe using BMP-2 (page 450, col. 1, last paragraph). Schmidmaier et al. describe using an immunoassay (ELISA) (abstract and page 454, col. 1, fourth paragraph), as stated in instant claims 16 and 17. Schmidmaier et al. describe contacting an osteogenic factor with a specific antibody and quantifying binding (page 454, col. 1, fourth paragraph), as stated in instant claim 18. Schmidmaier et al. describe quantifying in micrograms (page 451, col. 2, second paragraph), as encompassed in instant claim 19. Schmidmaier et al. describe a curve is established by correlating concentrations of at least one osteogenic factor with the percent released *in vivo* and *in vitro* (Figure 4).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the quantitative assessment the osteoinductivity of human demineralized bone matrix of Zhang et al. via the ELISA immunoassays of transforming growth factor-beta 1 (TGF-β1) of Schmidmaier et al. where the motivation would have been to

investigate the coating of implants with growth factors such as TGF-β1 to improve fracture healing as stated by Schmidmaier et al. (abstract and page 450, col. 2, third paragraph). The person of ordinary skill in the art would have expected success because growth factors, such as TGF, is known to have osteoinductive effects (Schmidmaier et al., page 449, col. 1, first paragraph).

Thus, Zhang et al. in view of Schmidmaier et al. make obvious claims 1, 3-6, 12-14, 16-20, 22-23, 31, and 37.

Claims 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Journal of Periodontology, 1997 Nov; Vol. 68(11), pages 1076-1084) as applied to claims 1, 3-6, 13, 19-20, 22-23, 31, and 37 above, and further in view of Urist (US 4,294,753).

Zhang et al. disclose the limitations of claims 1, 3-6, 13, 19-20, 22-23, 31, and 37, as stated in the 35 USC 102 rejection above. Zhang et al. do not disclose the limitations of claims 7-11.

Urist describes preparing chemical agents, such as bone morphogenetic protein (BMP), that cause bone tissue to form and grow (col. 1, second paragraph). Urist describes separating BMP and using it as a bone implant (col. 2, fourth paragraph) as well as implanting demineralized bone matrix (col. 1, fifth paragraph). Urist describes BMP is resistant to collagenase and isolating BMP in a digestive solution of collagenase (col. 2, first paragraph), as stated in instant claim 7. Urist describes demineralizing bone tissue, extracting BMP into a solution of solubilizing agent, separating the solubilizing agent from the solution, thereby precipitating and separating BMP in the aqueous medium (abstract; col. 1, ninth paragraph; and

Figure 1) which represents removing particulate debris, as stated in instant claim 8. Urist describes separating and purifying BMP via centrifugation (col. 5, last two paragraphs), as stated in instant claim 9. Urist describes demineralizing crushed bone by dialysis wherein BMP and other bone solids remain in the bag, the supernatant is filtered to remove cellular debris, cells and solid particles, and washed (col. 3, first paragraph) followed by admixing demineralized matrix with a salt and solubilizing agent which is then dialyzed to remove salt, solubilizing agent, and other impurities and precipitating BMP (col. 3, second and third paragraphs) which represents removing debris and interfering non-osteogenic factor molecules via dialyzing and precipitating, as stated in instant claims 8, 10, and 11. Urist describes further purifying the BMP precipitate and optional size exclusion fractionating (col. 3, fifth and sixth paragraphs and col. 4, first paragraph).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the quantitative assessment the osteoinductivity of human demineralized bone matrix of Zhang et al. via the removing of particulate debris and interfering non-osteogenic factors as stated by Urist, where the motivation would have been to separate and concentrate bone inducing agents like BMP, since the concentrated form of BMP improves the efficiency of the bone induction system, as stated by Urist (col. 1, second and ninth paragraphs). The person of ordinary skill in the art would have expected success because BMP is known to be used as an implant to fill bone defects, as stated by Urist (col. 2, second-to-last paragraph).

Thus, Zhang et al. in view of Urist make obvious claims 1, 3-11, 13, 19-20, 22-23, 31, and 37.

Claims 15 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (Journal of Periodontology, 1997 Nov; Vol. 68(11), pages 1076-1084) in view of Schmidmaier et al. (Journal of Biomedical Materials Research, 2001 May; Vol. 58(4), pages 449-455) as applied to claims 1, 3-6, 12-14, 16-20, 22-23, 31, and 37 above, and further in view of Long et al. (US 5,972,703).

Zhang et al. in view of Schmidmaier et al. describe the limitations of claims 1, 3-6, 12-14, 16-20, 22-23, 31, and 37, as stated in the 35 USC 103 rejection above. Zhang et al. in view of Schmidmaier et al. do not describe the limitations of claims 15 and 21.

Long et al. describe a demineralized bone matrix and how bone responds to bone specific growth factors, such as TGF-β and BMP (col. 3, second and third paragraphs). Long et al. describe studying tissue aggregate formation and correlating increased response of cells to improved availability of growth factor concentrations (col. 30, first paragraph), studying varying concentrations of osteogenic growth factors, including combinations of TGF- β and BMP, including BMP-2 (col. 30, second paragraph and col. 32, second paragraph), and studying combined effects of relevant cytokine and matrix molecules with optimal concentrations (col. 30, fourth paragraph), as stated in instant claims 15 and 21.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the quantitative assessment the osteoinductivity of human demineralized bone matrix of Zhang et al. via the ELISA immunoassays of transforming growth factor-beta 1 (TGF-β1) of Schmidmaier et al. where the motivation would have been to investigate the coating of implants with growth factors such as TGF-β1 to improve fracture healing as stated by Schmidmaier et al. (abstract and page 450, col. 2, third paragraph). It would

have been further obvious to a person of ordinary skill in the art at the time the invention was made to modify the methods of Zhang et al. and Schmidmaier et al. via studying combinations of growth factors as stated by Long et al., where the motivation would have been to study the role of differing growth factors on colony-forming cells to find therapeutic modalities that accelerate and/or complete the bone repair process after bone fractures, as stated by Long et al. (col. 1, second paragraph and col. 5, first paragraph). The person of ordinary skill in the art would have expected success because TGF-β and BMP-2 are known to be implicated in bone development, as stated by Long et al. (col. 3, second paragraph and col. 5, first paragraph).

Thus, Zhang et al. in view of Schmidmaier et al. and Long et al. make obvious claims 1, 3-6, 12-23, 31, and 37.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811.

October 10, 2006

Carolyn Smith
Examiner
AU 1631